

June 30, 2005

Timothy Adams, Ph.D.
Technical Contact
Eastman Chemical Company
100 North Eastman Road
Kingsport, TN 37662

Dear Dr. Adams:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for Ketone Bottoms (KB4/KB3) posted on the ChemRTK HPV Challenge Program Web site on March 2, 2004. I commend Eastman Chemical Company for its commitment to the HPV Challenge Program.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its Challenge Web site, EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

EPA will post this letter and the enclosed comments on the HPV Challenge Web site within the next few days. As noted in the comments, we ask that Eastman advise the Agency, within 60 days of this posting on the Web site, of any modifications to its submission. Please send any electronic revisions or comments to the following e-mail addresses: oppt.ncic@epa.gov and chem.rtk@epa.gov.

If you have any questions about this response, please contact Mark Townsend, Acting Chief of the HPV Chemicals Branch, at 202-564-8617. Submit questions about the HPV Challenge Program through the "Contact Us" link on the HPV Challenge Program Web site pages or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at tsca-hotline@epa.gov.

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

/s/

Oscar Hernandez, Director
Risk Assessment Division

Enclosure

cc: M. E. Weber
J. Willis

**EPA Comments on Chemical RTK HPV Challenge Submission:
Ketone Bottoms (KB4/KB3)**

Summary of EPA Comments

The sponsor, Eastman Chemical Company, submitted a test plan and robust summaries to EPA for Ketone Bottoms (KB3/KB4) (CAS No. 68990-20-5) dated December 30, 2003. EPA posted the submission on the ChemRTK HPV Challenge Website on March 2, 2004.

EPA has reviewed this submission and has reached the following conclusions

1. Physicochemical Data. The submitted data for these endpoints are adequate for the purposes of the HPV Challenge Program.
2. Environmental Fate. The submitter needs to provide measured ready biodegradation data for additional components to adequately address this endpoint.
3. Health Effects. EPA considers it inappropriate to use individual component data to characterize the toxicity of the two ketone bottom mixtures because of the uncertainty resulting from the absence of toxicity data on the significant undefined portion of each mixture. The submitter needs to conduct testing on KB4 and KB3 mixtures to adequately address these endpoints.
4. Ecological Effects. EPA agrees that fish acute toxicity data are adequate for the purposes of the HPV Challenge Program. The submitter needs to provide additional invertebrate and algae test data because the submitted data do not adequately represent the range of chemicals in the mixtures. EPA recommends that the submitter test a chemical within the C10-C12 range. Chronic daphnia toxicity data are needed for the most hydrophobic known component in the mixtures. The submitter needs to include some missing data elements in the robust summaries.

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.

EPA Comments on the Ketone Bottoms (KB4/KB3) Challenge Submission

Test Plan

Test Substance Identification

Ketone bottoms are presented as two mixtures (KB4 and KB3) under one CAS number. KB4 contains approximately 50% linear- and branched-chain C₉-C₁₂ aliphatic ketones. Other known constituents include mixed dimethylcyclohexanones (10.8%) and 6-methyl-2-heptanone (2.5%). The submitter anticipates the remaining ~37% of KB4 to be a complex mixture of ketones of similar molecular weight and structure. KB3 is a mixture of linear and branched-chain aliphatic ketones and alkyl-substituted cyclohexanones: >35% undecanone isomers, 11% cyclohexanone and 5% pentadecanone derivatives and other C₉-C₁₅ ketones.

Physicochemical Properties (melting point, boiling point, vapor pressure, partition coefficient and water solubility)

The submitted data for these endpoints are adequate for the purposes of the HPV Challenge Program.

Environmental Fate (photodegradation, stability in water, biodegradation, fugacity)

The data for photodegradation, stability in water, and fugacity are adequate for the purposes of the HPV Challenge Program.

Biodegradation. The experimental data provided by the submitter do not adequately describe the biodegradation behavior of the range of known components that make up the KB3 and KB4 substances. Experimental data on two analogues and estimated data (BIOWIN) on some components are not sufficient to address this endpoint for the purposes of the HPV Challenge Program because the biodegradation potential of the various ketone components will depend on chain length, degree of branching, carbonyl position and the presence of cyclic structures. The data provided by the submitter do not address these structural differences. The submitter needs to provide measured ready biodegradation data on enough components to address this variety of structures.

Health Effects (acute toxicity, repeated-dose toxicity, genetic toxicity, and reproductive/developmental toxicity)

The submitter needs to conduct testing using KB4 and KB3 mixtures to adequately address these endpoints.

The submitter provided no human health data for the mixtures KB4 and KB3 themselves. Although the submitter provided toxicity and metabolism data for selected components or their analogs, the test plan (1) did not adequately support the validity of using test data for individual components of a mixture for characterizing the toxicity of that mixture; (2) did not present a logical approach for integrating data for individual components of KB3/KB4 to qualitatively and quantitatively characterize the toxicity of these mixtures; and (3) did not present a means to address the uncertainty caused by the absence of toxicity data on the significant undefined portion of each ketone bottom mixture (~37% of KB4 and ~44% of KB3).

The test plan described some similarities in metabolism/excretion of the known ketone constituents of KB4 and KB3 and related chemicals to justify the use of analogs to represent individual component chemicals; however, it is not possible to predict whether such pathways pertain to the significant portion of each mixture that is not defined.

For example, the test plan (page 11) mentioned that 5-nonanone can be metabolized to a neurotoxic gamma-diketone, and that 5-nonanone is the only ketone in the KB4 mixture containing structural features that permit a neurotoxic gamma-diketone to form. The test plan also indicates that 5-nonanone when given to animals in a pure form at a certain dose level (233 mg/kg bw), did not show signs of general or neurological toxicity. However, when present in a mixture at this level (approximately 11%) it showed signs of neurotoxicity and peripheral neuropathy, suggesting that 5-nonanone acts as a synergist. Given the fact that approximately 37% of the KB4 mixture is not characterized and the uncertainty as to the potential for forming a neurotoxic gamma-diketone, EPA believes that testing on the mixture is warranted.

Most of the data presented for human health effects were for KB4 components or their analogs; no data were provided for components of KB3. Therefore, it does not appear possible to predict the human health effects of KB3 from existing submitted data.

Ecological Effects (fish, invertebrates, and algae)

Fish. EPA agrees that the data are adequate for the purposes of the HPV Challenge Program.

Invertebrates and Algae. The submitter needs to provide additional measured invertebrate and algae acute toxicity data because the submitted data do not represent the range of chemicals in the mixtures. EPA recommends that the submitter consider testing a chemical(s) in the C10-C12 range. In addition, chronic daphnia toxicity data are needed for the most hydrophobic known substance in each mixture that is accessible for testing.

Specific Comments on the Robust Summaries

Ecological Effects

Fish and Invertebrates. The submitter needs to include water solubility and log Kow input values in robust summaries for SAR data.

Followup Activity

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.